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Defective peroxisome biogenesis with a neuromuscular disorder resembling Werdnig-Hoffmann disease

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Article abstract—*Objective:* Characterization of the defect in a patient presenting a peripheral neuropathy with atypical features of distal motor involvement mimicking Werdnig-Hoffmann disease. *Patient:* Clinical signs included generalized hypotonia and floppiness, absence of stretch reflexes, muscle wasting, lack of head control and lingual fasciculations associated with unaffected facial muscles, and normal intellectual development. *Results:* Normal muscle histology ruled out Werdnig-Hoffmann disease. Elevated plasma concentrations of very long-chain fatty acids and bile acid intermediates combined with normal plasmalogen levels in erythrocytes suggested defective peroxisomal β-oxidation directly demonstrated by deficient pristanic acid and partially deficient C26:0 was present oxidation in cultured fibroblasts. Severely impaired pipecolic acid oxidation in liver and phytanic acid oxidation in fibroblasts was present. On light and electron microscopy of the liver tissue, rare peroxisomal membrane ghosts and trilamellar inclusions but absence of peroxisomes was noted. Immunoblot analysis revealed absence of peroxisomal β-oxidation enzymes in liver tissue but normal results in fibroblasts. Remarkably, expression of the peroxisomal defect in fibroblasts was indicated by the finding of mainly cytoplasmatic catalase, as in liver. Preliminary studies excluded classification of this patient within the large *PEX1* complementation group. *Conclusions:* The results suggest a novel peroxisome biogenesis disorder involving peroxisomal β-oxidation as well as phytanic and pipecolic acid oxidation rather than an isolated defect of peroxisomal β-oxidation. The association of a clinical picture mimicking Werdnig-Hoffmann disease with a novel peroxisomal disorder raises the question of whether investigation for peroxisomal function should be considered in every patient with an enigmatic spinal muscular atrophy-like syndrome.

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Most patients with inherited peroxisomal disorders present with severe disturbances of the nervous system.[1,2] Usually they are detected easily by additional clinical symptoms, such as errors of morphogenesis including dysmorphia and skeletal abnormalities, neurosensory defects, or hepatodigestive involvement. These three main early infantile categories of clinical symptoms roughly correspond to the original clinical descriptions, namely Zellweger syndrome (ZS), which is the most severe disorder combining all characteristic symptoms; neonatal adrenoleukodystrophy (NALD), which has a predominantly neurologic presentation; and infantile Refsum disease, which is the least severe disorder with predominance of hepatodigestive symptoms.[1,2] Biochemically, they are characterized by the loss of multiple peroxisomal functions and absence of morphologically distinguishable peroxisomes in hepatocytes and renal tubule cells[1,2] or peroxisome mosaicism.[3] Other peroxisomal disorders may present with similar symptoms but have an impairment of only a single or several peroxisomal functions and usually the presence of hepatic peroxisomes.[1,2]

In this report, we describe a unique patient presenting a peripheral neuropathy with atypical features of distal motor involvement mimicking Werdnig-Hoffmann disease that was later revealed as an original peroxisome biogenesis disorder.

Case report. This female child was born at term to consanguineous parents of Algerian origin after an uneventful pregnancy. Her weight was 3.2 kg, and Apgar scores were normal. Global hypotonia and moderate jaundice were noted. She was hospitalized several times in another hospital because of severe hypotonia and was then transferred to our hospital at the age of 5 months. She presented with severe generalized hypotonia and floppiness with predominant involvement of axial and distal muscles. The scarf sign was positive. Tendon stretch reflexes were absent, and there was severe muscle wasting. No pyramidal tract

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signs were found. She lacked head control but had good eye contact, was alert, and smiled upon stimulation. No dysmorphia was noted. Lingual fasciculations were constantly present. The girl showed normal awareness and mental development (determined by the Brunet-Lézine scale for psychomotor development in childhood). Given the clinical picture, Werdnig-Hoffmann disease was considered. Serum creatine kinase was normal. Nerve conduction velocity was within normal limits for age. EMG showed typical neurogenic changes predominantly in distal muscles with an increase in amplitude and duration of the motor unit potentials and an excess of polyphasic potentials. However, muscle histology was normal, and Werdnig-Hoffmann disease was ruled out.

In a more comprehensive evaluation, moderate hepatomegaly and impaired liver function reflected in elevated transaminases (aspartate aminotransferase 136 IU/L, alanine aminotransferase 155 IU/L; normal 5 to 20 for both values), prolonged prothrombin time (46%), and lowered coagulation factors (factor II 71%, factors VII + X 52%, factor V 87%) were found. Hypocholesterolemia (total cholesterol 2.15 mmol/L, normal 3.25 to 6.3; HDL cholesterol 0.26 mmol/L, normal >0.85; LDL cholesterol 1.53 mmol/L, normal 3.3 to 4.1) and lowered levels of plasma vitamin E (3.6 mg/L, normal 8 to 12) were present. An initial metabolic screening showed an abnormal organic acid profile with dicarboxylic aciduria suggesting a mitochondrial fatty acid oxidation defect, which was later ruled out (normal oxidation in fibroblasts). Chromatography of plasma and urine amino acids revealed an elevated pipecolic acid level and led to a complete peroxisomal investigation. A liver biopsy specimen showed mild periportal fibrosis associated with beginning neocanalicular proliferation and mild steatosis. On ophthalmologic examination bilateral cataracts were noted. Cerebral MRI, EEG, electroretinogram, and visual evoked potentials were normal at that time. Plasma vitamin A, total and free carnitine, and routine laboratory studies of red and white blood cells and electrolytes were within normal limits.

At 11 months she could sit, pass objects from one hand to the other, and pronounce several words. According to the peroxisomal investigation (table 1) and given the probable role of docosahexaenoic acid (DHA) in the pathogenesis of peroxisome biogenesis disorders,[4] a treatment with DHA (100 mg/h, later 200 mg/24 h) and a diet low in phytanic acid was started. However, major hypotonia with severe amyotrophy persisted, and progressive psychomotor retardation began. At 15 months strabismus and retinitis pigmentosa with abnormal electroretinogram were noted. Hearing remained normal. Skeletal radiography showed severe osteoporosis. At 27 months she went on a holiday to Algeria where DHA treatment was stopped. She had a severe gastrointestinal infection with dehydration, loosing almost 2 kg of weight and deteriorating rapidly. Coming back to Paris she was hospitalized close to her home and later transferred to our hospital. On admittance she was in a severely deteriorated state, especially for cognitive functions. After an initial recovery she suddenly died without explanation. No autopsy was performed.

Methods. Very long-chain fatty acids (VLCFAs); phytanic, pristanic, and pipecolic acid; and bile acid intermediates were measured in plasma according to previously described methods.[5] Polyunsaturated fatty acids and plasmalogens were measured by capillary column gas chromatography after direct transesterification of plasma and erythrocytes, as specified elsewhere.[6]

Liver and skin biopsies were performed for diagnostic purposes after informed consent of the parents. Peroxisomal functions were determined in cultured fibroblasts by assaying phytanic α-oxidation,[7] peroxisomal β-oxidation, dihydroxyacetone phosphate acyltransferase (DHAPAT) activity, de novo plasmalogen synthesis, and concentrations of VLCFAs as previously described.[8-10] Cross-reactive immunologic material to the peroxisomal β-oxidation enzymes acyl-CoA oxidase and 3-oxoacyl-CoA thiolase in fibroblasts and liver tissue was examined by an immunoblotting procedure as described by Wanders et al.[11] L-pipecolic acid oxidation was investigated in liver as described by Wanders et al.[12]

Peroxisomes were made visible in the liver tissue for light and electron microscopy by staining for catalase activity[13] and by protein A-colloid gold immunolocalization of the matrix proteins catalase, acyl-CoA oxidase, 3-ketoacyl-CoA thiolase, and alanine/glyoxylate aminotransferase (AGT), as well as 43-kd peroxisomal membrane protein.[14] Morphometry of peroxisomes was performed on random electron micrographs with a semi-automated device.[15]

The cultured skin fibroblasts were fused essentially according to Brul et al.[16] The fused cells were cultured for 3 days on minimum essential medium (DMEM) without fetal calf serum (FCS), after which the occurrence of complementation was tested with pristanic acid β-oxidation.[8]

Results. The results of biochemical analyses reflecting peroxisomal metabolism in this patient are given in table 1. The increased levels of VLCFAs and bile acid intermediates combined with an elevated pristanic/phytanic acid ratio and normal plasmalogen levels in erythrocytes pointed to a disorder of peroxisomal β-oxidation, as directly demonstrated by deficient pristanic acid and partially deficient C26:0 β-oxidation in cultured fibroblasts (see table 1). In addition, pipecolic acid was highly elevated in plasma (but not in urine) due to severely impaired pipecolic acid oxidation in liver tissue (see table 1). As expected, de novo plasmalogen synthesis and DHAPAT activity in fibroblasts were normal (see table 1). Immunoblotting studies in liver tissue showed absence of the 50-kd and 20-kd components of acyl-CoA oxidase and 41-kd thiolase, whereas in fibroblasts normal results were found (table 2). Remarkably, virtually all catalase was cytoplasmatic, indicating that the peroxisomal defect was indeed expressed in fibroblasts.

Light and electron microscopy of the liver tissue disclosed absence of peroxisomes with cytoplasmic and nuclear localization of catalase and AGT (figure 1). Very rare peroxisomal membrane ghosts with the approximate size of normal peroxisomes were identified by their immunoreactivity for a 43-kd peroxisomal membrane protein (electron micrograph of such an organelle in reference 14, figure 7). Sometimes these membranes formed double or triple layers, enclosing little or no contents. Many fine insoluble fat droplets were present in nonparenchymal cells together with small birefringent inclusions. Enlarged periodic–acid-Schiff- and acid phosphatase-positive macrophages were found. There was massive fatty infiltration in the parenchyma, and beginning cirrhosis was seen. By electron microscopy typical trilamellar inclusions were found in parenchymal and nonparenchymal cells (figure 2).

Table 1 *Biochemical analysis reflecting peroxisomal disorder*

Parameter	Patient	Controls	Zellweger syndrome
Plasma			
$C_{26:0}$ (μmol/L)	4.21	0.22–1.31	1.18–1.77
$C_{26:0}/C_{22:0}$ ratio	0.25	0.003–0.021	0.056–0.76
Trihydroxycholestanoic acid (μmol/L)	0.48	0–0.035	0.11–47.2
Dihydroxycholestanoic acid (μmol/L)	1.414	0–0.012	0.32–44.1
Pipecolic acid (μmol/L)	346	0.54–2.46	7.53 –391
Phytanic acid (μmol/L)	36.2	0.01–9.88	0.52 –118
Pristanic acid (μmol/L)	20.6	0.01–2.98	0.10–34.7
Pristanic acid/phytanic acid ratio	0.57	0.05–0.40	0.08–0.44
Docosahexaenoic acid (DHA) (μmol/L)	20.66	94.09 ± 36.64	NA
Plasmalogens (μmol/L)	25.84	69.13 ± 30.95	NA
Urine			
Pipecolic acid (mmol/mol creatinine)	20	1.2–24.1	20.2–270
Erythrocytes			
DHA (pmol/10^6 cells)	7.47	37.78 ± 13.59	NA
Plasmalogens (pmol/10^6 cells)	38.77	54.72 ± 6.26	NA
Fibroblasts			
De novo plasmalogen biosynthesis			
% pPE in PE	88.3	64.5–85.7	4.6–55.4
% pPC in PC	9.2	2.0–8.0	0.4–1.2
$^3H/^{14}C$-ratio in alkenyl PE	1.6	0.3–2.4	6.4–63.1
$^3H/^{14}C$-ratio in alkenyl PC	0.6	0.3–2.0	3.1–10.9
DHAP-AT (nmol/2 hr/mg)	10.2	5.9–15.9	0–1.6
C26:0 (μg/mg protein)	0.14	0.02–0.10	0.21–1.21
C26:0/C22:0 ratio	0.07	0.03–0.07	0.21–1.07
C26:0 β-oxidation (pmol/min/mg protein)	381	1,002 ± 336	117 ± 82
Pristanic acid β-oxidation (pmol/min/mg protein)	61	1,147 ± 325	12 ± 12
Phytanic acid α-oxidation (pmol/min/mg protein)	10.2	68 ± 13	<10
Catalase immunofluorescence	Diffuse	Particle bound	Diffuse
Liver			
Pipecolic acid oxidation (pmol/h/mg protein)	14	400 ± 38	<1

Values are represented as means ± SD or as ranges.

NA = not available; pPE = plasmalogen phosphatidylethanolamine; PE = total phosphatidylethanolamine; pPC = plasmalogen phosphatidylcholine; PC = total phosphatidylcholine; DHAP-AT = dihydroxyacetone phosphate acyltransferase.

Preliminary complementation studies to establish the genetic relationship between our patient and other peroxisomal disorders revealed that our patient does not belong to the large complementation group with *PEX1* deficiency.[17,18] Further complementation studies to classify our patient are under way (see Note added in proof).

Discussion. The rapid expansion of the clinical spectrum of peroxisome-related diseases constitutes a widening diagnostic challenge.[1,19] According to recent recommendations, biochemical investigation of peroxisomal functions is warranted if a patient has one or more of the following abnormalities: craniofacial, neurologic (hypotonia, seizures, peripheral neuropathy), neurosensory (visual or hearing abnormalities), hepatic, skeletal, and digestive with hypocholesterolemia and failure to thrive.[1,20] The reported patient presented with a neurologic picture strikingly similar to Werdnig-Hoffmann disease and initially did not arouse suspicion of peroxisomal disease. Typical clinical symptoms of Werdnig-Hoffmann disease included generalized hypotonia and floppiness, absence of stretch reflexes, muscle wasting, lack of head control and lingual fasciculations associated with unaffected facial muscles, and normal intellectual development.[21] The neurogenic changes in EMG studies as well as normal serum creatine kinase were compatible with the diagnosis

Table 2 *Immunoblotting studies on cultured fibroblasts and liver tissue*

	Fibroblasts		Liver tissue	
Protein studied	Patient	Control	Patient	Control
Acyl-CoA oxidase				
70 kd	+	+	+	+
50 kd	+	+	−	+
20 kd	+	+	−	+
3-oxoacyl-CoA thiolase				
41 kd	+	+	−	+
44 kd	−	−	+	−

of Werdnig-Hoffmann disease. However, our patient had involvement of predominantly distal muscles rather than proximal and axial muscles, as is most commonly observed in Werdnig-Hoffmann disease. Furthermore she later learned to sit and control her head, whereas patients with early onset Werdnig-Hoffmann disease usually show progressive worsening

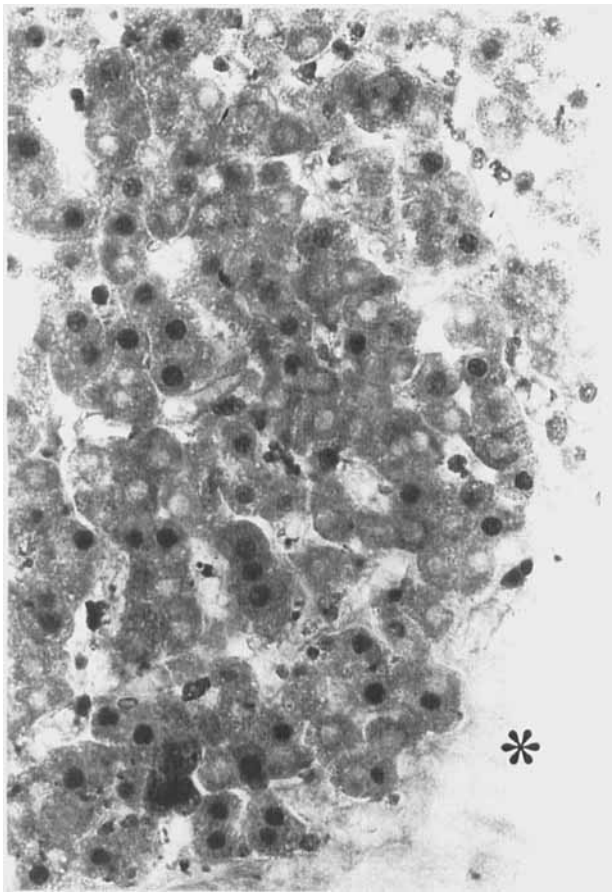

Figure 1. Diffuse cytoplasmatic localization of alanine/glyoxylate aminotransferase in the liver parenchymal cells; also, many parenchymal nuclei are immunoreactive. Granules indicating a peroxisomal localization of the antigen are not observed; nonparenchymal tissue (asterisk) shows no reaction. A similar localization was found for catalase, reflecting the typical distribution of peroxisome biogenesis disorders. Magnification ×400.

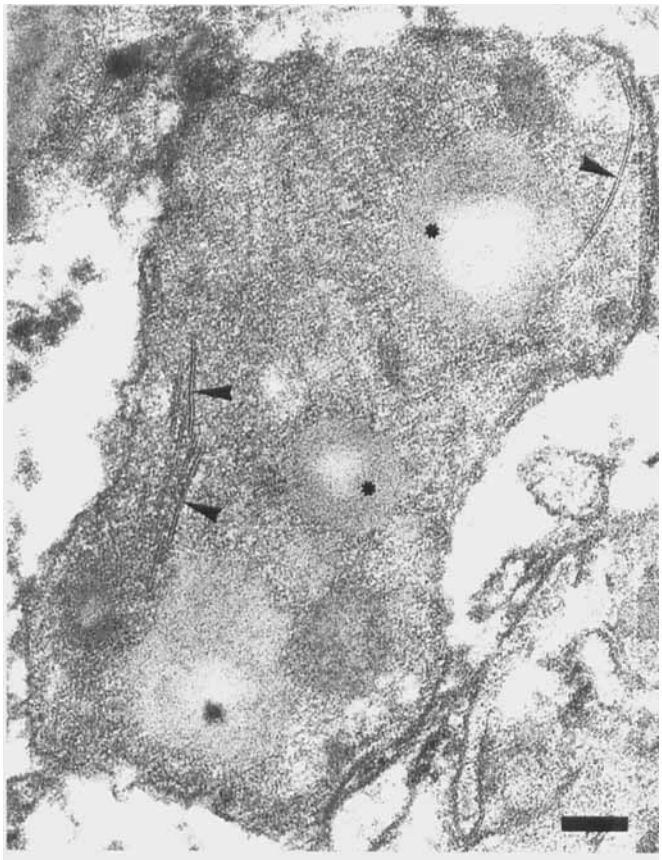

Figure 2. Electron micrograph showing equidistant (rigid) trilamellar inclusions (arrowheads) in a liver parenchymal lysosome, which also contains insoluble fat droplets (asterisk). Scale bar = 0.2 μm; magnification ×45,000.

of neurologic symptoms and die early.[21] Conversely, mental development had slowed down in our patient at the age of 1 year, whereas in Werdnig-Hoffmann disease intelligence is preserved. Finally, other clinical features unusual for Werdnig-Hoffmann disease such as cataracts and hepatopathy were present, raising serious doubts as to this diagnosis. Normal morphology of muscle definitely ruled out Werdnig-Hoffmann disease.

The unique finding in our patient is that accumulation of VLCFAs and bile acid intermediates combined with normal plasmalogen levels in erythrocytes point to an isolated defect of peroxisomal β-oxidation. Conversely, absence of genuine liver peroxisomes, accumulation of trilamellar inclusions, and deficient phytanic and pipecolic acid oxidation suggest a peroxisome biogenesis disorder (table 3).

A generalized peroxisomal disorder such as classic ZS or NALD is excluded by the finding of normal plasmalogen levels in erythrocytes and normal de novo plasmalogen synthesis and DHAPAT activity in fibroblasts. It is tempting to explain this normal plasmalogen synthesis by the presence of rare but normally sized peroxisomal membrane ghosts in the liver; indeed the enzymes involved are membrane-bound. However, the increased plasma concentrations of VLCFAs and bile acid intermediates

Table 3 *Current scheme of peroxisomal defects*

	Zellweger syndrome ↓	Patient ↓	Isolated β-oxidation disorder
VLCFAs	↑	↑	↑
Bile acids	↑	↑	N–↑
Pipecolic acid	↑	↑	N
Phytanic acid	↑	↑	N–↑
Pristanic acid	↑	↑	↑
Pristanic/phytanic	N	↑	↑
Plasmalogens	↓	N	N
Liver peroxisomes on microscopy	Absent	Absent	Present
Molecular defect	Biogenesis disorder: generalized loss of peroxisomal functions	Biogenesis disorder: loss of multiple peroxisomal functions	Single enzyme defect: loss of a single peroxisomal function
Other examples	Infantile Refsum disease, neonatal ALD	Rhizomelic chondrodysplasia punctata	Refsum disease, X-linked ALD

VLCFAs = very long-chain fatty acids; N = normal; ALD = adrenoleukodystrophy.

combined with an elevated pristanic/phytanic acid ratio are suggestive of a defect in peroxisomal β-oxidation, as directly demonstrated by deficient pristanic and partially deficient C26:0 β-oxidation in cultured fibroblasts. The elevation of bile acid intermediates in our patient is an important clue to the site of a possible defect because normal concentrations of bile acid intermediates were found in two siblings with isolated acyl-CoA oxidase deficiency,[22] whereas they were abnormal in isolated deficiencies of peroxisomal bi(tri)functional protein[23] and peroxisomal thiolase.[24]

Apart from these well-characterized patients, an increasing number of patients have been described with a defect in peroxisomal β-oxidation of unknown etiology and detectable enzyme proteins.[2,19,25] Most were considered to have an enzyme protein without catalytic activity. However, in contrast to these patients, liver peroxisomes in our patient were ultrastructurally not distinguishable after staining for marker enzymes, peroxisomal β-oxidation proteins were absent on immunoblot analysis, and pipecolic acid oxidation was impaired, all of which is in favor of a generalized peroxisomal disorder (see table 3). The enzymatic organization of the peroxisomal fatty acid β-oxidation pathway remains incompletely understood. There are two acyl-CoA oxidases with specificity for straight-chain[26] and branched-chain fatty acyl-CoA esters.[27] The view that the subsequent steps are catalyzed by one bifunctional protein and one peroxisomal thiolase is no longer tenable.[28] Recently, Wanders et al.[29] provided evidence that there are separate pathways for the oxidation of straight-chain and branched-chain fatty acids. The findings of severely deficient pristanic acid β-oxidation and less severe deficiency of C26:0 β-oxidation suggest a defect in the pathway of branched-chain rather than straight-chain fatty acids in the present case.

The expression in fibroblasts in our patient is bizarre; although immunoblot analysis showed the presence of acyl-CoA oxidase and 3-oxoacyl-CoA thiolase enzyme proteins, deficient pristanic acid and partially deficient C26:0 β-oxidation with a mildly abnormal VLCFA profile were found, indicating that at least one of the peroxisomal β-oxidation enzymes must be immunologically intact but catalytically inactive. Remarkably, virtually all catalase was cytoplasmatic, indicating that the peroxisomal defect was definitely expressed in fibroblasts. Differences between cultured fibroblasts and a liver sample have been reported in other peroxisomal patients.[3]

The findings in our patient are different from those for any of the patients described in the literature so far, and it is difficult to know what the actual defect is. Overall, the results suggest a disorder of peroxisome biogenesis involving peroxisomal β-oxidation, phytanic acid α-oxidation, and pipecolic acid oxidation rather than an isolated defect of peroxisomal β-oxidation. However, the scheme of peroxisomal β-oxidation as used today may be too simplistic, and more enzymes may yet be identified. Additional studies are under way to reveal the underlying defect in our patient.

Whatever the basic defect is, we stress that prenatal diagnosis is possible in such undefined peroxisomal disorders. Indeed, prenatal diagnosis was successfully made in a younger, healthy brother of the present patient by measuring VLCFAs and bile acid intermediates in amniotic fluid.[5]

Returning to the clinical aspects, we emphasize that in our patient elevated pipecolic acid on screening amino acid chromatography finally led to a complete peroxisomal investigation that revealed the unique peroxisomal disorder. DHA treatment resulted in only minor biochemical improvement (results not shown) and no clinical improvement. The association of DHA ethyl ester with a very low phytanic acid diet may have influenced the potential of DHA in our patient by neutralizing its effects.[4] Given that the interruption of DHA therapy coincided with

a severe intermittent illness (gastroenteritis and dehydration), a deleterious effect of this interruption in our patient seems rather unlikely, but cannot be ruled out.

The association of a clinical picture mimicking Werdnig-Hoffmann disease with an original peroxisomal disorder raises the question of whether investigation for peroxisomal function should be considered in every patient with an enigmatic spinal muscular atrophy-like syndrome.

Note added in proof. Complementation studies have now shown that the gene affected in this patient is the *PEX12* gene, which is one of many different genes involved in peroxisomal biogenesis mutated in one of the complementation group (C63). See Reference 30.

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